DETAILED ACTION

Applicant's response received on 5/9/11 has been entered. Claims 1-5, 7-10, 12-13, 16-22, and 40 remain pending and under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Information Disclosure Statement

The information disclosure statement (IDS) filed on 5/9/11 meets the requirements of 37 CFR 1.97 and 1.98 and has been considered by the examiner. An initialed and signed copy of the 1449 is attached to this action.

Claim Rejections - 35 USC § 103

The rejection of claims 1-5, 7-10, 12-13, 16, and 40 under 35 U.S.C. 103(a) as being unpatentable over WO 00/34494 (2000), hereafter referred to as Schlom et al., in view of WO 01/24832 (2001), hereafter referred to as Pecher, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant reiterates their arguments that Schlom et al. does not teach a poxvirus vector encoding both MUC and CEA or a prime-boost protocol with two poxvirus vectors each

encoding MUC and CEA and that Pecher et al. does not supply the missing teachings because Pecher does not teach a single vector encoding MUC and CEA, and further does not exemplify the co-administration of a vector encoding MUC and a vector encoding CEA.

In response, the rejection of record clearly states that Schlom et al. teaches the administration of more than one dose of recombinant poxvirus encoding a tumor antigen, such as MUC1 or CEA, or a prime and boost delivery method where a first vector is administered followed by an administration of a second vector, where the first and second vectors are different strains of poxvirus (Schlom et al., in particular page 39). The rejection of record further states that Schlom et al. teaches that the poxvirus vector can encode **more than one** tumor associated antigen, and/or further encode a cytokine such as GM-CSF (Schlom et al., pages 5, 31-37). The only teaching missing from Schlom et al. is a specific teaching to choose MUC1 and CEA as the tumor associated antigens to express together in a recombinant poxvirus vector. Pecher was cited to supplement Schlom et al. by teaching the combined administration of vectors, including vaccinia virus vectors, encoding MUC1 and CEA to human patients for the treatment of tumors (Pecher et al. pages 4-6). Pecher was not cited for teaching a single vector encoding MUC and CEA. Schlom et al. already provides the teaching that the poxvirus can encode more than one tumor associated antigen, and Pecher was cited for providing the motivation to choose the combination of MUC1 and CEA to express in a single poxvirus vector as taught by Schlom et al. Likewise, Schlom et al. already provides the teachings for treating breast cancer. Further, there is no requirement that Pecher et al. actual exemplify co-administration of MUC1 and CEA in order for Pecher et al. to provide motivation to combine the administration of vectors encoding MUC1 and CEA. Pecher et al. clearly teaches throughout the publication, including the claims, to

administer both a vector encoding MUC1 and a vector encoding CEA to treat tumors. Therefore, it is reiterated that in view of the teachings of Schlom et al. to use poxvirus vectors encoding more than one target tumor associated antigen for the treatment of cancers including breast cancer, and the motivation provided by Pecher to co-administer vectors encoding MUC1 and CEA to treat human tumors, it would have been *prima facie* obvious to the skilled artisan at the time of filing to make and use a single poxvirus vector encoding MUC1, CEA, and TRICOM (B7, ICAM-1, and LFA-1) in the methods of treating cancer, such as breast cancer, taught by Schlom et al.. Further, based on the detailed guidance provided by Schlom et al. for making poxvirus vectors which encode multiple heterologous genes, and the successful demonstration by Schlom et al. that poxvirus encoding tumor antigens such as CEA and MUC1 can successfully prevent tumor growth, the skilled artisan at the time of filing would have had a reasonable expectation of success in treating breast cancer using the methods of Schlom et al. as modified by Pecher et al.

The applicant further reiterates their argument that the skilled artisan would not have been motivated to a prepare a vector encoding two tumor associated antigens because of potential competition between the two antigens resulting in reduced immune responses, citing Palmowski et al., and Brody et al., made of record with the previous response. The applicant also reiterates that there are "unexpected benefits" to the present invention which would have been nonobvious at the time of filing, referring again to Gully et al., and Tsang et al., of record.

In response, the applicant is again reminded that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Examples of attorney

statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. MPEP 716.01(c). MPEP 716.02(g) further states: "The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements or representations made are correct, as provided by 35 USC 25 and 18 U.S.C. 1001." Permitting a publication to substitute for expert testimony would circumvent the guarantees built into the statute. *Ex parte Gray*, 10 USPQ2d 1922, 1928 (Bd. Pat. App. & Inter. 1989). Publications may, however, be evidence of the facts in issue and should be considered to the extent that they are probative. With this in mind, the pre- and post-filing publications cited in applicant's response have been considered.

The post-filing reference by Gulley et al. has been addressed in detail in the previous office actions which stated that while Gully et al. reports the practice of one embodiment of the method as claimed in human patients, there are no teachings in Gulley et al. that the co-expression of MUC1 and CEA resulted in "unexpected" or surprising results. In fact, while Gulley et al. on page 3060 suggests that vectors directed against multiple TAAs may evoke additive or synergistic immune responses, Gulley et al. does not report any additive or synergistic responses using the MUC1/CEA TRICOM vaccine. On the contrary, on page 3068, Gulley et al. remarks that a previous trial using a CEA TRICOM vaccine reported greater CEA specific T cell responses than those observed in the MUC1/CEA TRICOM trial. Therefore, Gulley et al. does not support applicant's argument for unexpected results.

Tsang et al. was also considered in the previous office action. The post-filing reference Tsang et al. provides preliminary *in vitro* test results for two different poxvirus vectors each comprising 5 transgenes encoding MUC1,CEA, B7, ICAM-1, and LFA-1 and demonstrates that dendritic cells infected with either poxvirus stimulates T cells against both the MUC1 and CEA antigens. Tsang et al. does not disclose any results from *in vivo* methods as claimed nor does Tsang et al. state that their *in vitro* results were surprising or unexpected. As such, Tsang et al. does not support applicant's argument for unexpected results.

From the above analysis, neither of the post-filing references provide any comparative data suggesting or demonstrating that the administration of a single poxvirus encoding MUC1 and CEA is unexpectedly more effective than the administration of two separate vectors, or that the skilled artisan would not have expected that the single vector encoding MUC1 and CEA would be capable of stimulating anti-tumor immune responses.

Finally, the references cited by the applicant which are part of the prior art published before applicant's filing date do not support applicant's argument that skilled artisan at the time of filing would not have expected that administration of a single poxvirus encoding MUC1 and CEA would stimulate the immune system against the CEA and MUC1 antigens. Brody et al. is a 1972 report about the phenomenon of antigen competition when administering protein antigen fragments. Brody et al. is silent as to immunization with MUC1 or CEA or the use of poxvirus to administer either or both of these antigens. Palmowski et al., a more recent article, discusses ways to improve the immune response to multiple antigens in a prime-boost strategy. However, Palmowski et al. clearly shows that the initial administration of a single vector encoding more than CTL peptide epitope was clearly effective in stimulating CTL against all of the encoded

peptide epitopes. While Palmowski et al. showed that boosting with the same vector results in a higher immune response to some epitopes versus other epitopes contained within the vector, this result does not change the fact that the skilled artisan would have had a reasonable expectation that one or more administrations of the same or two different poxvirus vectors encoding both MUC1 and CEA would be capable of inducing an immune response against a breast tumor expressing these antigens. The applicant is reminded that the claims as written contain no limitations as the specific characteristics of the immune response generated, and neither the working example provided nor the post-filing references discussed above demonstrate that practice of the method as claimed produces an immune response against the poxvirus encoded MUC1 or CEA that was unexpected or surprising.

Thus, for the reasons set forth above, the rejection of record stands.

The rejection of claims 17-22 under 35 U.S.C. 103(a) as being unpatentable over WO 00/34494 (2000), hereafter referred to as Schlom et al., in view of WO 01/24832 (2001), hereafter referred to as Pecher, as applied to claims 1-5, 7-10, 12-13, 16, and 40 above, and further in view of Grosenbach et al. (2001) Cancer Research, Vol. 61, 4497-4505, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

Applicant's arguments concerning the teachings of Schlom et al. and Pecher et al. have been addressed in detail above and have not been found persuasive. In regards to Grosenbach et al., the applicant states that Grosenbach et al. only discloses the administration of CEA, and not CEA and MUC1. However, as discussed above and in the rejection of record, Schlom et al.

teaches to make a poxvirus vector encoding more than one tumor antigen and to administer the vector to treat cancer, specifically breast cancer, and Pecher et al. was cited to provide motivation to choose MUC1 and CEA as the tumor antigens to use in the methods of Schlom et al. Grosenbach et al. was cited to supplement Schlom et al. and Pecher by teaching a vaccine strategy for administering poxvirus encoding tumor associated antigen and TRICOM that synergistically amplifies tumor antigen specific immune responses. Specifically, Grosenbach et al. teaches that a prime/boost strategy where a orthopox vaccinia virus encoding CEA and TRICOM is administered once followed by three boosts of a fowlpox encoding CEA and TRICOM substantially enhances tumor antigen specific immune responses (Grosenbach et al., pages 4501-4503).

Therefore, it is maintained that in view of the teachings of Schlom et al. to administer different strains of poxvirus encoding more than one tumor associated antigen, such as MUC or CEA, and TRICOM in a prime boost strategy, the motivation provided by Pecher to co-express MUC and CEA for tumor therapy, and the particular motivation provided by Grosenbach et al. to prime using one dose of vaccinia encoding tumor antigen and TRICOM and boost with multiple doses of a fowlpox encoding tumor antigen and TRICOM, it would have been *prima facie* obvious to the skilled artisan at the time of filing to administer a priming dose of an orthopox such as vaccinia, or other well known modified vaccinia such as NYVAC or MVA as taught by Schlom, encoding MUC1, CEA, and TRICOM followed by boosting with multiple doses of fowlpox encoding MUC1, CEA, and TRICOM to a patient at risk for or having a breast tumor with a reasonable expectation of success in preventing or delaying tumor growth.

Thus, for the reasons set forth above, the rejection of record stands.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for

electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

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